COMPOSITIONS CONTAINING, METHODS INVOLVING, AND USES OF NON-NATURAL AMINO ACID LINKED DOLASTATIN DERIVATIVES

CROSS REFERENCE

[0001] This application claims priority to U.S. Provisional Application No. 61/491,146, entitled, "Compositions Containing, Methods Involving, and Uses of Non-Natural Amino Acid Linked Dolastatin Derivatives," filed May 27, 2011, the contents of which are incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

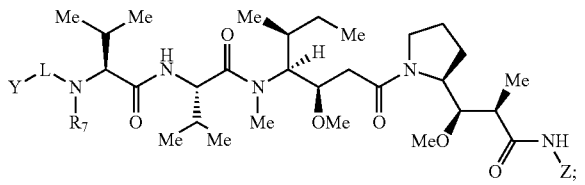
[0002] The ability to incorporate non-genetically encoded amino acids (i.e., "non-natural amino acids") into proteins permits the introduction of chemical functional groups that could provide valuable alternatives to the naturally-occurring functional groups, such as the epsilon $—NH_2$ of lysine, the sulfhydryl —SH of cysteine, the imino group of histidine, etc. Certain chemical functional groups are known to be inert to the functional groups found in the 20 common, genetically-encoded amino acids but react cleanly and efficiently to form stable linkages with functional groups that can be incorporated onto non-natural amino acids.

[0003] Methods are now available to selectively introduce chemical functional groups that are not found in proteins, that are chemically inert to all of the functional groups found in the 20 common, genetically-encoded amino acids and that may be used to react efficiently and selectively with reagents comprising certain functional groups to form stable covalent linkages.

SUMMARY OF THE INVENTION

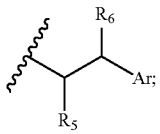
[0004] Disclosed herein are toxic moieties with one or more linker(s), toxic groups linked to non-natural amino acids, and methods for making such non-natural amino acids and polypeptides.

[0005] Some embodiments of the present invention describe a compound, or salt thereof, comprising Formula (I):


(I)

wherein:

[0006] Z has the structure of:



[0007] R_5 is H, COR_8, C_1-C_6alkyl, or thiazole;

[0008] R_5 is OH or NH-(alkylene-O)$_n$—NH_2;

[0009] R_6 is OH or H;

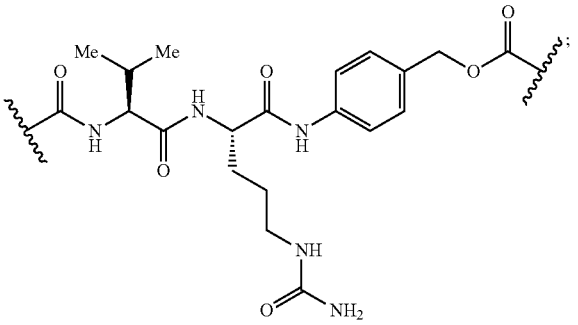
[0010] Ar is phenyl or pyridine;

[0011] R_7 is C_1-C_6alkyl or hydrogen;

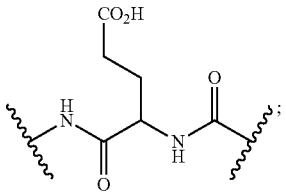
[0012] Y is selected from the group consisting of an hydroxylamine, methyl, aldehyde, protected aldehyde, ketone, protected ketone, thioester, ester, dicarbonyl, hydrazine, amidine, imine, diamine, azide, keto-amine, keto-alkyne, alkyne, cycloalkyne, and ene-dione;

[0013] L is a linker selected from the group consisting of alkylene-, -alkylene-C(O)—, -(alkylene-O)$_n$-alkylene-, -(alkylene-O)$_n$-alkylene C(O), (alkylene-O)$_n$—$(CH_2)_n$—NHC(O)—$(CH_2)_n$—C(Me)$_2$-S—S—$(CH_2)_{n'''}$—NHC(O)-(alkylene-O)$_{n''''}$ alkylene-, -(alkylene-O)$_n$-alkylene-W-, -alkylene-C(O)—W-, -(alkylene-O)$_n$-alkylene-U-alkylene-C(O), and -(alkylene-O)$_n$-alkylene-U-alkylene-;

[0014] W has the structure of:



[0015] U has the structure of:



[0016] or L is absent, Y is methyl, R_5 is COR_8, and R_8 is —NH-(alkylene-O)$_n$—NH_2; and each n, n', n", n''' and n'''' are independently integers greater than or equal to one.

[0017] In some embodiments, R_5 is thiazole. In other embodiments, R_6 is H. In certain embodiments, Ar is phenyl. In further or additional embodiments, R_7 is methyl. In some embodiments, n is an integer from 0 to 20, 0 to 10 or 0 to 5.